This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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</table>
| Individuals:  
• With conditions requiring warfarin treatment | Interventions of interest are:  
• Genetic testing to determine warfarin dose | Comparators of interest are:  
• Standard care without genetic testing | Relevant outcomes include:  
• Test accuracy  
• Test validity  
• Other test performance measures  
• Morbid events  
• Medication use  
• Treatment-related morbidity |

Description

Variants in CYP2C9 and VKORC1 genes result in differences in warfarin metabolization. Using information about an individual’s CYP2C9 and VKORC1 genotypes, as well as other known characteristics, to personalize starting dose may reduce the time to warfarin dose stabilization and avoid serious bleeding events.

Summary of Evidence

The evidence for genetic testing to determine warfarin dose in patients who have a warfarin treatment regimen includes randomized controlled trial (RCTs), systematic reviews of RCTs, and cohort studies. Relevant outcomes are test accuracy and validity, other test performance measures, morbid events, medication use, and treatment-related morbidity. Although the evidence supports a strong association between genetic variants and stable warfarin dose, and, to a lesser extent, between genetic variants and international normalized ratio and bleeding outcomes, the evidence is not sufficient to conclude that testing for CYP2C9 and VKORC1 (and possibly CYP4F2) genetic variants improves health outcomes. Genetic testing may help predict the initial warfarin dose within the first week of warfarin treatment, but the evidence, including several meta-analyses of RCTs, does not provide consistent evidence that clinically relevant outcomes (e.g., bleeding rates, thromboembolism) are improved. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

Genotyping to determine cytochrome p450 2C9 (CYP2C9) and vitamin K epoxide reductase subunit C1 (VKORC1)
genetic polymorphisms is considered **investigational** for the purpose of managing the administration and dosing of warfarin, including use in guiding the initial warfarin dose to decrease time to stable international normalized ratio and reduce the risk of serious bleeding.

**Medicare Advantage**

This service may be considered **medically necessary** for Medicare Advantage members, but only if enrolled in a qualifying Clinical Trial.

**Background**

Warfarin is administered for preventing and treating thromboembolic events in high-risk patients; warfarin dosing is a challenging process, due to the narrow therapeutic window, variable response to dosing, and serious bleeding events in 5% or more of patients (depending on definition). Patients are typically given a starting dose of 2 to 5 mg and monitored frequently with dose adjustments until a stable international normalized ratio (INR) value (a standardized indicator of clotting time) between two and three is achieved. During this adjustment period, a patient is at high risk of bleeding.

Stable or maintenance warfarin dose varies among patients by more than an order of magnitude. Factors influencing stable dose include body mass index, age, interacting drugs, and indication for therapy. In addition, genetic variants of cytochrome p450 2C9 (CYP2C9) and vitamin K epoxide reductase subunit C1 (VKORC1) genes together account for a substantial proportion of inter-individual variability. More recently, a single nucleotide polymorphism (change in a single base-pair in a DNA sequence) in the **CYP4F2** gene has been reported to account for a small proportion of the variability in stable dose; **CYP4F2** encodes a protein involved in vitamin K oxidation.

Using the results of **CYP2C9** and **VKORC1** genetic testing to predict a warfarin starting dose that approximates a patient’s likely maintenance dose may benefit patients by decreasing the risk of serious bleeding events and the time to stable INR. Algorithms have been developed that incorporate not only genetic variation but also other significant patient characteristics and clinical factors to predict the best starting dose.

**Regulatory Status**

Several tests to help assess warfarin sensitivity by determining presence or absence of the relevant **CYP2C9**, **VKORC1**, and **CYP4F2** variants have been cleared by the U.S. Food and Drug Administration (FDA) for marketing. Similar tests also may be available as laboratory-developed services; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act. The tests are not all the same in terms of the specific variants and number of variants detected. Generally, such tests are not intended as stand-alone tools to determine optimum drug dosage but should be used along with clinical evaluation and other tools, including the international normalized ratio, to predict the initial dose that best approximates the maintenance dose for patients.

On August 16, 2007, FDA approved updated labeling for Coumadin®, to include information on genetic testing for gene variants that may help “personalize” the starting dose for each patient and reduce the number of serious bleeding events. The label was updated again on January 22, 2010. With each update, manufacturers of warfarin (generic for Coumadin®) were directed to add similar information to their products’ labels. The 2010 update added information on personalizing initial dose according to genotyping results for **CYP2C9** and **VKORC1**, providing a table of genotypes and suggested initial dose ranges for each. However, suggested starting doses also are provided for when genotyping information is unavailable, indicating that genetic testing is not required.
Furthermore, FDA did not include information on genetic variation in the label’s black box warning regarding bleeding risk.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. *Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.*

**References**

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


